PATENT SPECIFICATION

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International Classification:—C07d.

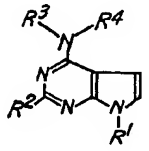
COMPLETE SPECIFICATION

Pyrrolo[2,3-d]Pyrimidine Derivatives and the manufacture thereof

We, THE WELLCOME FOUNDATION LIMITED, a British Company of 183—193 Euston Road, London, N.W.1 do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to novel amino-derivatives of pyrrolo[2,3-*d*]pyrimidine and the manufacture thereof.

It has been discovered that the compounds of formula (I) have pharmacological activity in the mammal.

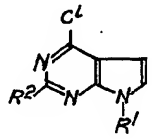


(I)

In this and subsequent formulae R^1 is a hydrogen atom or a methyl group, R^2 is a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R^3 is a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms and R^4 is an alkyl, alkenyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, carboxyalkyl, dialkylaminoalkyl or aralkyl group having not more than 14 carbon atoms, or NR^3R^4 is a pyrrolidino, piperidino or morpholino group or an N^1-alkylpiperazino group in which the alkyl group has from 1 to 4 carbon atoms.

The compounds of formula (I) are conveniently prepared by heating a 4-chloropyrrolo-[2,3-*d*]pyrimidine of formula (II) with an amine of the formula HNR^3R^4.

[*Price 4s. 6d.*]



(II)

The 4-chloropyrrolo[2,3-*d*]pyrimidines of formula (II) are described and claimed in British patent specifications 812,366 and 32973/61 (Serial No. 915,304).

The pharmacological activity of the compounds of formula (I) is apparently exerted on various regions of the nervous system. Different effects are exhibited by various groups of the compounds, as explained and illustrated below.

The compounds of formula (I) in which each of R^1 and R^2 is a hydrogen atom, R^3 is a hydrogen atom or a methyl group and R^4 is an alkyl group having from 1 to 4 carbon atoms have hypotensive effects, produced or accompanied by vasodilatation. Coronary vasodilatation particularly is a prominent feature of their effects.

The compounds of formula (I) in which each of R^1, R^2 and R^3 is a hydrogen atom and R^4 is an alkyl group having from 5 to 10 carbon atoms have hypnotic and anticonvulsant activities. 4 - n - Nonylaminopyrrolo[2,3-*d*]-pyrimidine is especially active as an anticonvulsant.

The compounds of formula (I) in which each of R^1, R^2 and R^3 is a hydrogen atom or a methyl group and R^4 is an ω-alkoxyalkyl or ω,ω-dialkoxyalkyl group have muscle relaxant, anticonvulsant and tranquillising activities.

The compounds of formula (I) in which R^1 and R^3 are hydrogen atoms and R^4 is an aralkyl group, particularly those in which R^2 is a methyl group and R^4 is a benzyl group having not more than 8 carbon atoms, have anticon-

vulsant or tranquillising and muscle relaxant activities. 2-Methyl-4-benzylaminopyrrolo-[2,3-*d*]pyrimidine is especially active as a tranquilliser and muscle relaxant.

The compounds of formula (I) in which NR^3R^4 is an N^1-methylpiperazino or N^1-ethylpiperazino group have tranquillising activity.

The compounds of formula (I) can be obtained in the form of the free base or an acid addition salt. These forms of the compound can be regarded as equivalent if the acid addition salt contains pharmaceutically acceptable anions.

The following examples illustrate the invention. The products were isolated in the form of the free base except where indicated otherwise. Temperatures are in degrees Celsius.

EXAMPLE 1.

A solution of 4-chloropyrrolo[2,3-*d*]-pyrimidine (1.3 g.) and n-propylamine (2.5 ml.) in absolute ethanol (30 ml.) containing one drop of concentrated hydrochloric acid was heated in a metal bomb at 125° for 7 hours. The bomb was cooled and its contents were evaporated to dryness on the steam bath. The residual thick oil was triturated with 2.5% w/v sodium hydroxide (5 ml.) and allowed to stand at room temperature until crystallisation occurred. The solid obtained by filtration (1.2 g.) was recrystallised from 30% aqueous ethanol with added decolourising charcoal to give 4 - n - propylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 162°.

EXAMPLE 2.

A solution of 2-methyl-4-chloropyrrolo-[2,3-*d*]pyrimidine (0.9 g.) and n-amylamine (2.4 ml.) in 25 ml. of absolute ethanol containing one drop of concentrated hydrochloric acid was heated at 140° for 7 hours in a metal bomb. The bomb was cooled and its contents evaporated to a thick oil on the steam bath. The oil crystallised upon trituration with 5 ml. of 2.5% sodium hydroxide. The solid (1.1 g.), after filtering and drying over calcium chloride in a desiccator, was recrystallised from 25% aqueous ethanol with added decolourising charcoal to give 2-methyl-4-n-amylamino-pyrrolo[2,3-*d*]pyrimidine, m.p. 157—159°.

EXAMPLE 3.

A solution of 7-methyl-4-chloropyrrolo-[2,3-*d*]pyrimidine (1 g.) and n-amylamine (1.5 ml.) in absolute ethanol (25 ml.) containing 1 drop of concentrated hydrochloric acid was heated in a bomb at 130° for 6 hours. After cooling, the contents of the bomb were evaporated to dryness and the solid was triturated with sodium hydroxide. It was recrystallised by dissolution in hot benzene followed by the addition of hexane to a permanent turbidity. On chilling, 7-methyl-4-n-amylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 125—127°, crystallised and was recovered by filtration.

EXAMPLE 4.

A solution of 4 - chloropyrrolo[2,3-*d*]-pyrimidine (1.7 g.) and pyrrolidine (3 g.) in 95% ethanol (35 ml.) was heated in a bomb at 130° for 6 hours. The solvent was evaporated and the oily residue was dissolved in water (60 ml.) at pH 2.0 by the addition of a 1:1 dilution of hydrochloric acid. A small amount of black tar was filtered off and the filtrate was adjusted to pH 10.0 to give 4-pyrrolidino-pyrrolo[2,3-*d*]pyrimidine (1.7 g.) m.p. 263—265°, as a white amorphous precipitate.

The products of the following examples were prepared from the appropriate amine and a 4-chloropyrrolo[2,3-*d*]pyrimidine by methods similar to those described in Examples 1 to 4.

5. 4 - Methylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 231—232°.

6. 4 - Ethylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 205°.

7. 2 - Methyl - 4 - ethylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 189—190°.

8. 7 - Methyl - 4 - ethylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 159°.

9. 4 - Isopropylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 170°.

10. 4 - n - Butylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 145—146°.

11. 4 - Isobutylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 173—174°.

12. 4 - s - Butylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 125—126°, crystallised from benzene.

13. 4 - t - Butylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 183°, crystallised from benzene.

14. 4 - n - Amylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 129—130°, crystallised from benzene-heptane by the method of Example 3.

15. 4 - Isoamylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 166—167°, crystallised from benzene-heptane by the method of Example 3.

16. 4 - s - Amylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 140—141°.

17. 4 - Cyclopentylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 162—163°.

18. 4 - Allylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 167°.

19. 4 - β - Methoxyethylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 167—168°, crystallised from heptane.

20. 2 - Methyl - 4 - β - methoxyethylamino-pyrrolo[2,3-*d*]pyrimidine, m.p. 144—146°.

21. 4 - γ - Methoxypropylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 144—145°.

22. 4 - Dimethylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 222°.

23. 4 - *N* - Methyl - *N* - ethylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 170°.

24. 4 - *N* - Methyl - *N* - n - propylamino-pyrrolo[2,3-*d*]pyrimidine, m.p. 148—149°.

25. 4 - *N* - Methyl - *N* - isopropylamino-pyrrolo[2,3-*d*]pyrimidine, m.p. 156—157°.

26. 4 - *N* - Methyl - *N* - n - amylamino-pyrrolo[2,3-*d*]pyrimidine, m.p. 133—135°.

27. 4 - Diethylaminopyrrolo[2,3-*d*]pyrimi-dine, m.p. 174—175°.

28. 4 - Di - n - propylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 118°.

29. 4 - Piperidinopyrrolo[2,3-*d*]pyrimidine, melting to a clear oil at 184—185°.

EXAMPLE 30.

4 - Chloropyrrolo[2,3-*d*]pyrimidine (1.2 g.) and n-nonylamine (5 g.) were refluxed in water (50 ml.) for 2 hours. The mixture was treated with 5% aqueous sodium hydroxide (4 ml.), chilled for two hours, and filtered. After drying in the desiccator, the solid (2.55 g.) was recrystallised from hot aqueous ethanol yielding 4 - n - nonylaminopyrrolo[2,3-*d*]-pyrimidine (2 g.), m.p. 122—124°, as a hemihydrate.

EXAMPLE 31.

2 - Methyl - 4 - chloropyrrolo[2,3-*d*] pyrimidine (1.0 g.) and benzylamine (4.0 g.) were refluxed in water (50 ml.) for 3 hours. Ethanol was slowly added, while heating, until complete solution was attained. The solution was chilled overnight and 2-methyl-4-benzylaminopyrrolo[2,3-*d*]pyrimidine (1.4 g.), m.p. 205—207°, was filtered off.

EXAMPLE 32.

2 - Methyl - 4 - chloropyrrolo[2,3-*d*]-pyrimidine (2.0 g.) and *N*-methylpiperazine (5.0 g.) were refluxed in water (65 ml.) for 2 hours. Then potassium hydroxide (3 g.) was added and when dissolved the clear solution was chilled overnight yielding a primary crop (2 g.) of 2 - methyl-4-N^1-methylpiperazinopyrrolo[2,3-*d*]pyrimidine as a dihydrate. A second crop (0.35 g.) was obtained by slowly evaporating off one-half of the mother liquor. Recrystallisation from n-heptane yielded a hemihydrate, m.p. 191—192°.

EXAMPLE 33.

4 - Chloropyrrolo[2,3-*d*]pyrimidine (1.2 g.) and *N*-ethylpiperazine (4 g.) were heated in water (50 ml.) at 85—90° for 2 hours. Then potassium hydroxide (3.5 g.) was dissolved in the reaction mixture and the solution was chilled overnight. Upon filtration 4-N^1-ethylpiperazinopyrrolo[2,3-*d*]pyrimidine (1.5 g.) was obtained as a dihydrate. Drying for 1.5 hours at 135° gave a hemihydrate. The compound changed in crystalline form at 150—160° and melted to a clear oil at 175°.

The products of the following examples were prepared from the appropriate amine and a 4 - chloropyrrolo[2,3-*d*]pyrimidine by methods similar to those described in Examples 30 to 33.

34. 4 - n - Hexylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 150—151°, crystallised from heptane.

35. 4-Isohexylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 129—130°.

36. 4 - n - Heptylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 135°, crystallised from heptane.

37. 4 - n - Octylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 118—119°, crystallised from heptane.

39. 4 - n - Decylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 110—111°.

40. 4 - Cyclohexylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 149—151°.

41. 4 - Benzylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 196°.

42. 2 - n - Propyl - 4 - benzylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 161—162°.

43. 2,7 - Dimethyl - 4 - benzylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 147—148°.

44. 2 - Methyl - 4 - *p* - methylbenzylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 211°.

45. 2 - Methyl - 4 - *m* - methylbenzylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 184—185°; hydrochloride m.p. 230—236°.

46. 2 - Methyl - 4 - *p* - methoxybenzylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 189—191°.

47. 4 - Phenethylaminopyrrolo[2,3-*d*]-pyrimidine, m.p. 197—198°; hydrochloride, m.p. 231—234°.

48. 2 - Methyl - 4 - phenethylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 208—209°.

49. 4 - β - Dimethylaminoethylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 164—165°.

50. 4 - β - Diethylaminoethylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 146—147°.

51. 4 - β - Hydroxyethylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 209°.

52. 2 - Methyl - 4 - γ - isopropoxypropylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 139—140°.

53. 4 - β,β - Diethoxyethylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 124—126°, crystallised from benzene-heptane by the method of Example 3.

54. 2 - Methyl - 4 - β,β - diethoxyethylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 129—130°.

55. 4 - γ,γ - Diethoxypropylaminopyrrolo-[2,3-*d*]pyrimidine, m.p. 120—121°.

56. 4 - Carboxymethylaminopyrrolo[2,3-*d*]-pyrimidine, which turned pink at 230°, and decomposed completely at 265—270° with evolution of gas.

57. 4 - *N* - Methyl - *N* - β,β - diethoxyethylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 127—129°.

58. 2 - Methyl - 4 - *N* - methyl - *N* - β,β-diethoxyethylaminopyrrolo [2,3-*d*] pyrimidine, m.p. 155°.

59. 4 - *N* - Methyl - *N* - γ,γ - diethoxypropylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 87—89°.

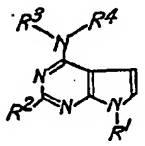
60. 4 - *N* - Ethyl - *N* - carboxymethylaminopyrrolo[2,3-*d*]pyrimidine, m.p. 204°.

61. 4 - Morpholinopyrrolo[2,3-*d*]pyrimidine, m.p. 215°.

62. 4 - N^1 - methylpiperazinopyrrolo-[2,3-*d*]pyrimidine, m.p. 142°.

WHAT WE CLAIM IS:—

1. A compound of formula (I)



(I)

wherein R^1 is a hydrogen atom or a methyl group, R^2 is a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R^3 is a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms and R^4 is an alkyl, alkenyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, carboxyalkyl, dialkylaminoalkyl or aralkyl group having not more than 14 carbon atoms, or NR^3R^4 is a pyrrolidino, piperidino or morpholino group or an N^1-alkylpiperazino group in which the alkyl group has from 1 to 4 carbon atoms.

2. A compound claimed in Claim 1 in which each of R^2 and R^3 is a hydrogen atom or a methyl group and R^4 is an alkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl or dialkylaminoalkyl group.

3. A compound claimed in Claim 2 in which R^1 and R^2 are hydrogen atoms and R^4 is an alkyl group having from 1 to 4 carbon atoms.

4. 4 - Ethylaminopyrrolo[2,3-*d*]pyrimidine.

5. 4-n-Propylaminopyrrolo[2,3-*d*]pyrimidine.

6. 4-t-Butylaminopyrrolo[2,3-*d*]pyrimidine.

7. 4 - *N* - Methyl - *N* - n - propylaminopyrrolo[2,3-*d*]pyrimidine.

8. A compound claimed in Claim 2 in which R^1, R^2 and R^3 are hydrogen atoms and R^4 is an alkyl group having from 5 to 10 carbon atoms.

9. 4-n-Octylaminopyrrolo[2,3-*d*]pyrimidine.

10. 4-n-Nonylaminopyrrolo[2,3-*d*]pyrimidine.

11. A compound claimed in Claim 2 in which R^4 is an ω-alkoxyalkyl or ω,ω-dialkoxyalkyl group.

12. 4 - β - Methoxyethylaminopyrrolo[2,3-*d*]pyrimidine.

13. 2 - Methyl - 4 - β - methoxyethylaminopyrrolo[2,3-*d*]pyrimidine.

14. 4 - β,β - Diethoxyethylaminopyrrolo[2,3-d]pyrimidine.

15. 4 - *N* - Methyl - *N* - γ,γ - diethoxypropylaminopyrrolo[2,3-*d*]pyrimidine.

16. 2 - Methyl - 4 - *N* - methyl - *N* - β,β-diethoxyethylaminopyrrolo[2,3-*d*]pyrimidine.

17. A compound claimed in Claim 1 in which R^1 and R^3 are hydrogen atoms and R^4 is an aralkyl group.

18. A compound claimed in Claim 17 in which R^2 is a methyl group and R^4 is a benzyl group having not more than 8 carbon atoms.

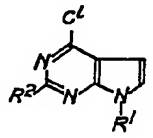
19. 2 - Methyl - 4 - benzylaminopyrrolo[2,3-*d*]pyrimidine.

20. A compound claimed in Claim 1 in which NR^3R^4 is an N^1-methylpiperazino or N^1-ethylpiperazino group.

21. 4 - N^1 - Ethylpiperazinopyrrolo[2,3-*d*]-pyrimidine.

22. 2 - Methyl - 4 - N^1 - methylpiperazinopyrrolo[2,3-*d*]pyrimidine.

23. A method of preparing a compound claimed in any preceding claim wherein a 4-chloropyrrolo[2,3-*d*]pyrimidine of formula (II)



(II)

is heated with an amine of the formula HNR^3R^4.

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